Remarks

Claim 1 is amended to recite a natural or synthetic polysaccharide. Support for the amendment is found, for example, on page 12, lines 9-12 of the specification.

Claim 2 is amended to recite dextrans, alginates, and their derivatives provided the polysaccharide chains have an amount of saccharide ranging from 2 to 2000 units. Support for the amendment is found, for example, at page 13, lines 3-12 of the specification.

Claim 3 is amended to recite that the saccharide units in a *synthetic* polysaccharide are connected by an acetal, hemiacetal, ketal, orthoester, amide, ester, carbonate or carbamate bond. Support for the amendment is found, for example, at page 7, lines 23-25 of the specification.

Claim 6 is amended to correct a typographical error.

Claims 8 and 17 are amended to recite that the oligoamine is either spermine or alkyl-substituted spermine, wherein the alkyl substituent contains 1-6 carbons. Support for the amendment is found, for example, at page 8, lines 1-10.

Claim 15 has been amended to delete the phrase "predetermined type of".

Claim 19 has been amended to more clearly define the pharmaceutical carrier as an amphiphilic cationic and/or non-ionic lipid combined with cationic and non-ionic polymers. Support for the amendment is found, for example, on page 16, line 20 to page 17, line 5 of the specification.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 2, 3, 5, 6, 10-13, 15-17, and 19 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary skill in the pertinent art at the time the invention was made. The test for definiteness under 35 U.S.C. 112, second paragraph is whether those skilled in the art would understand what is claimed when the claim is read in light of the specification. (*Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)).

Claim 2 has been amended to more clearly define the members of the Markush group. The Examiner stated that the recitations "dextrans" and "alginates" are seen to include derivatives, which have not been particularly pointed out or distinctly claimed and therefore the metes and bounds of the derivatives cannot be sufficiently determined. One of ordinary skill in the art would recognize that the terms "dextrans" and "alginates" refer to dextran and alginate polymers of different molecular weights, i.e. different number of saccharide monomer units. The applicant discloses that the polysaccharide must contain between 2 and 2000 saccharide units.

The Examiner states that claim 3 is unclear because the saccharide units in a polysaccharide are generally connected via ether linkages. Claim 3 has been amended to recite *synthetic* polysaccharides, in which the saccharide units can be connected by a linkage other than an ether linkage.

Claims 8 and 17 have been amended to recite that the oligoamine is either spermine or alkyl-substituted spermine, wherein the alkyl substituent contains 1-6 carbons. Therefore, the metes and bounds of the derivatives can be determined by one of ordinary skill in the art using the applicant's disclosure.

Claims 10 and 11 recite the term "oligomers". An oligomer is defined as a molecule of intermediate relative molecular mass, the structure of which essentially comprises a small plurality of units derived, actually or conceptually, from molecules of lower relative molecular mass (IUPAC Recommendations on Nomenclature, 1996). The applicant discloses a biodegradable polycation composition having an amphiphilic residue wherein the amphiphilic residue is selected from the group consisting of fatty chains, phospholipids, cholesterols, ethylene glycol oligomers, propylene glycol oligomers and combinations thereof. One of ordinary skill in the art would recognize that the terms "ethylene glycol oligomers" and "propylene glycol oligomers" refer to polymers of ethylene and propylene glycol comprising a small number (i.e. 2 to 10) of monomer units.

Claim 10 further recites the term "cholesterol derivatives". Example 8 on page 45, line 28, of the specification describes the conjugation of cholesterol to hydrophilic polysaccharides.

In addition, on pages 23 and 26, the specification discloses a number of derivatives of cholesterol, including Cholesteryl chloroformate, Cholesteric acid N-hydroxy succinimide (NHS) ester, di-Chol-L-Lysine-NHS, and di-Chol-L-Lysine-OMe. Furthermore, a number of papers disclosing cholesterol derivatives were published well before the filing of the current application (see, for example, Farhood H et al., "Effect of cationic cholesterol derivatives on gene transfer and protein kinase C activity" in *Biochim Biophys Acta.* 1111(2):239-46 (1992) and Vigneron JP et al., "Guanidinium-cholesterol cationic lipids: efficient vectors for the transfection of eukaryotic cells" in *Proc. Natl. Acad. Sci. USA* 93(18):9682-6 (1996), copies of which are enclosed). Therefore, one of ordinary skill in the art would understand what is claimed by the applicants when the claim is read in light of the specification.

Claim 15 has been amended to delete the phrase "predetermined type of". Claim 15 recites a biodegradable polycation composition further comprising a ligand for facilitating binding the composition to a cell or tissue.

Claim 19 defines the pharmaceutically acceptable carrier as a mixture of an amphiphilic cationic and/or non-ionic lipid and cationic and non-ionic polymers.

Rejection Under 35 U.S.C. § 102

Claims 1, 5, 7, 12-16, and 18 were rejected under 35 U.S.C. § 102(b) as being anticipated by WO 93/25239 by Jung et al. ("Jung"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

A claim is anticipated only if each and every element is found, either expressly or inherently described, in a single prior art reference (*Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)).

The applicant claims a biodegradable polycation composition associated with an anionic molecule comprising a ***linear*** polysaccharide chain having an amount of saccharide units ranging from 2 to 2000; and at least one oligoamine directly grafted to the linear polysaccharide chain per each segment of 5 saccharide units wherein the oligoamine has at least two amine groups and wherein the oligoamine has a molecular weight up to 1000 daltons.

Jung describes the preparation of derivatives of arabinogalactan which can be used to target therapeutic agents to cells possessing the asialoglycoprotein receptor. A preferred embodiment is a composition comprising arabinogalactan and poly-L-lysine as a carrier for genes or antisense oligonucleotides used in parenteral administration (page 9, lines 9-13). Poly-L-lysine has a molecular weight between 1000 and 4000 daltons.

Arabinogalactan is a polysaccharide composed of D-galactose and L-arabinose wherein the galactose and arabinose residues are coupled via β-1,3 linkages. Arabinogalactan is ***highly branched*** with the side chains containing galactose and arabinose units of various lengths at practically every residue of the backbone. Jung discloses that the underivatized 4-hydroxy group on galactose and the clustering of suitable sugars, as is displayed by highly branched polysaccharides such as arabinogalactan, are important factors in binding the asiaglycoprotein receptor (page 6, lines 32-36). In contrast, Jung discloses that glucose and mannose do not

interact with the asialoglycoprotein receptor. Thus, arabinogalactan is distinguishable from *linear* polysaccharides containing glucose or mannose such as dextrans, starches, celluloses, inulins, and β-1,4 linked galactan in its ability to bind to the asiaglycoprotein.

Finally, Jung does not disclose a composition in which at least one oligoamine is directly grafted to the linear polysaccharide chain *per each segment of 5 saccharide units* and wherein the oligoamine has a molecular weight *up to 1000* daltons. Therefore, the claims as amended are not anticipated by Jung.

Rejection Under 35 U.S.C. § 103

Claims 1, 2, 4, 6, 8, 9, 17, and 18 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 93/25239 by Jung *et al.* ("Jung"), in combination with Russian Patent No. 2027190 to Autenshlyus *et al.* ("Autenshlyus")) and U.S. Patent No. 6,011,008 to Domb ("Domb"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable

expectation of success must be both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed previously, Jung discloses the preparation of derivatives of arabinogalactan which can be used to target therapeutic agents to cells possessing the asialoglycoprotein receptor. However, Jung does not disclose a biocompatible polycation composition containing a ***linear*** polysaccharide and at least one oligoamine directly grafted to the linear polysaccharide chain per each segment of 5 saccharide units and wherein the oligoamine has a molecular weight up to 1000 daltons.

Autenshlyus discloses a polysaccharide antigen-*poly*ethyleneimine conjugate as an immunosorbent for detection of streptococcus and pneumococcus infections wherein the polyethyleneimine has a molecular weight of at least 30,000 daltons. However, Autenshylus does not disclose a biocompatible polycation associated with an anionic macromolecule. Further, Autenshlyus does not disclose a biocompatible polycation composition containing a linear polysaccharide and at least one *oligoamine* directly grafted to the linear polysaccharide per each segment of 5 saccharide units wherein the oligoamine has a molecular weight up to 1000 daltons.

Domb discloses a water-soluble conjugate of a polysaccharide and an unoxidized, oxidation-sensitive bioactive substance wherein the bioactive substance is conjugated to the polysaccharide via an imine bond. However, Domb does not disclose a biocompatible *polycation* composition associated with an anionic macromolecule containing a linear

polysaccharide and at least one oligoamine directly grafted to the linear polysaccharide and wherein the oligoamine has at least two amino groups and a molecular weight up to 1000 daltons.

Autenshlyus and Domb do not disclose the elements missing from Jung. Accordingly, the claims as amended are not obvious over Jung in combination with Autenshlyus and Domb.

Double Patenting Rejection

Claims 1-19 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of copending Application Serial No. 10/044,538 ("the '538 application"). The Examiner alleges that 1, 2, 3, and 19 of the '538 application are drawn to the same polycation composition as claims 1, 16 and 19 of the present application. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a copending application, the disclosure of the copending application may not be used as prior art.

Claim 2 of the '538 application is drawn to a biodegradable polycation complex with a polyanion comprising a polysaccharide chain having an amount of saccharide ranging from 2 to 2000 saccharide units, at least one oligoamine having at least two amino groups grafted to the polysaccharide chain per each segment of 5 saccharide units *and* at least one further grafted group, which is hydrophobic or amphiphilic, grafted to the polysaccharide chain per each

segment of 50 saccharide units, wherein the hydrophobic or amphiphilic group includes an aliphatic chain of at least 4 carbon atoms.

Claim 1 of the present application is drawn to a biodegradable polycation composition comprising a *linear* polysaccharide chain having an amount of saccharide units ranging from 2 to 2000, and at least one oligoamine having at least two amino groups *directly* grafted to the linear polysaccharide chain per each segment of 5 saccharide units, wherein the oligoamine has a molecular weight up to 2000 daltons.

The Examiner alleges that the recitations in claim 1 of the '538 application are seen in claim 2 of the present applications. Such an assertion is incorrect. The biodegradable polycation compositions recited in claim 1 of the present application does not contain a hydrophobic or amphiphilic group grafted covalently to the polysaccharide chain per each segment of 50 saccharides. Further, the polycation composition of the present application comprises a *linear* polymer. Such a limitation is not recited in the claims of the '538 application. Finally, the polycation composition of the present application comprises at least one oligoamine having at least two amino groups grafted *directly* to the linear polysaccharide chain per each segment of 5 saccharide units, and wherein the oligoamine has a molecular weight up to 1000 daltons. The polycation composition described in the claims of the '538 application does no recite that the oligoamine is grafted directly to the polysaccharide chain or that the oligoamine has a molecular weight up to 1000 daltons.

The compositions of the present application contain new and distinguishable limitations over the compositions of the copending '538 applications. Therefore, the compositions of the present application are not obvious over the compositions of the copending '538 application.

Allowance of claims 1-19, as amended, is respectfully solicited.

Respectfully submitted,

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Date: August 24, 2004

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